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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,021	08/06/2001	Yongming Sun	DEX-0150	7327

26259 7590 03/10/2003

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/762,021	Applicant(s) Sun et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 12, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) *2-11* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed December 13, 2002 (Paper No. 13) in response to the Office Action of November 13, 2002 (Paper No. 12) is acknowledged and has been entered. It is noted that due to an apparent inadvertent error, claim 6, SEQ ID NO:1 was included in Group 1. However it is clear, given that the inventive group was described as a method of diagnosing colon cancer comprising assaying for a CSG protein and that Applicant elected Group 1 drawn to diagnosing colon cancer comprising assaying for a CSG protein, that claim 6 which is drawn to CSG wherein the CSG comprises SEQ ID NO:1 which is a nucleic acid is not intended to be part of this group. Therefore, claim 6 has been removed from the Group 1 and is found properly in Group 4. Further, it is noted that Groups 2 and 3 are also drawn to methods for diagnosing the presence of colon cancer in a patient comprising assaying for CSG protein. Each of these groups also improperly includes claim 6 which is found properly in Groups 5 and 6 respectively. Thus, Groups 1-3, without claim 6 and drawn only to a method for diagnosing the presence of colon cancer in a patient comprising assaying for CSG protein are hereby rejoined. Claims 1-11 are pending in the application and Claims 2-11 and all limitations drawn to any inventions other than methods of diagnosing colon cancer comprising assaying for a CSG protein have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claim 1 drawn to method of diagnosing colon cancer comprising assaying for a CSG protein is currently under prosecution.

2. Applicant's election with traverse of Group 1, claims 1 and 6 drawn to method of diagnosing colon cancer comprising assaying for a CSG protein

expressed by SEQ ID NO:1 is acknowledged. It is noted that Claim 6 has been withdrawn from consideration for the reasons set forth above. The traversal is on the ground(s) that the (a) multiple Groups listed by Examiner have unity of invention in the combination of categories set forth, for example, the antibodies of Groups 37-39 are useful in the processes of Groups 40-45, (b) the inventions have not been shown to be independent or distinct and the examination of all groups would not impose a serious burden on the examiner and that in particular the CSGs of Groups 1-3 would reveal art relating to mRNAs or genes for these proteins as well as uses thereof as set forth in Groups 5-45, (c) the Examiner has provided no evidence that the Groups have acquired separate status in the art.. The arguments have been considered but have not been found persuasive (a')(b')(c') Groups 1-3 have been rejoined as set forth above and further as previously set forth, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention, after that, all other products and methods will be broken out as separate groups, (b') the inventions have been shown to be independent or distinct in that Groups 4-45 are drawn either to other processes or to products not used in the process of Group 1, whose search, given the complex nature of the art, would be an undue burden on the Examiner and on the Office search, since different searches and issues are involved in the examination of each group (c') given the independent or distinct nature of the inventions under the cited PCT articles, it is clear that the Groups have acquired separate status in the art. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

3. In view of Applicant's election of a method for diagnosing the presence of colon cancer in a patient comprising assaying for CSG protein encoded by SEQ ID NO:1, Applicant is invited to amend claim 1 to include this limitation. Further it is noted that, in the interests of compact prosecution, although not presently claimed, a colon cancer diagnostic assay for the protein encoded by SEQ ID NO:1 has been addressed in section 5(C) below.

Claim Objections

4. Claim 1 is objected to because it recites non-elected limitations. Appropriate correction and amendment of the claim is required.

Claim Rejections - 35 USC § 112

5. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method of diagnosing colon cancer comprising assaying levels of CSG protein in a patient and comparing the measured levels of CSG protein with levels in cells, tissues or bodily fluids from a normal human control, wherein an increase in measured levels in said patient compared with normal human control is associated with the presence of colon cancer. Since the claim is drawn to CSG protein in a patient, it is assumed for examination purposes that the invention is drawn to an *in vivo* imaging diagnostic assay.

The specification teaches that an increase in CSG in the patient versus the normal human control is associated with the presence of colon cancer (p. 7, lines 1-

4). Typically, a positive result for the patient being tested for cancer is one in which cells, tissues or bodily fluid levels of CSG is at least two times, most preferably at least five times higher than the same cells, tissues or bodily fluid of a normal human control (p. 7, lines 5-10). The specification teaches that labeled antibodies against a CSG can be injected into a patient for radioimmunoscintographic imaging (p. 13, lines 1-30). The specification exemplifies quantitiation of mRNA expression of three CSGs by PCR wherein mRNA expression of 81 cancer tissues was compared to matched normal control tissues as well as quantification of relative levels of mRNA expression in commercially pooled samples. A review of the 81 cited examples reveals that in 63 individual cases, that is in 78% of the cases, CSG mRNA expression level was decreased in the cancer tissue as compared with the matched normal control. The specification further reveals CSG mRNA expression levels of 3 CSGs wherein the expression level is 238, 10,000 and 2486 compared with testis which is designated as 1 (pages 16-31).

One cannot extrapolate the teaching of the specification to the enablement of the claim because:

(A) Although the cited mRNAs encode putative proteins, there is no teaching of whether any protein product is actually produced. It is well known in the art that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M. Et al, 1995, Pediatric Res., 37(6):681-686). Further, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition,

1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if the exemplified CSG mRNA could in fact be translated into a polypeptide expression product. Further, It would be expected that the commercial CSG mRNA samples are pooled from numerous subjects and that the levels here, compared to testis reflect the average mRNA expression of the CSGs in a relatively large population of normal ascending colon. It is noted that in a comparison of the

matched individual normal with these pooled samples it appears that the matched normal individual samples do not even come close to the average amount of mRNA expressed in the commercially available pooled samples. It is not clear why there is this difference and it is not clear whether or not the matched normal controls from cancer patients are in any way related to normal controls, thus it is not even clear how the mRNA assays could or should be evaluated. Finally, a review of Tables 1-3 reveals that in 63 out of the 81 cases, the matched normal control number was higher than the number for the cancer tissue, that is, the amount of CSG mRNA was decreased compared with normal control. Thus, even if a protein were produced and even if the protein production was commensurate in scope with mRNA production, no one of skill in the art would believe it more likely than not that the claimed invention would reliably function as claimed since there would be, based on the data in the specification, a 77% false negative rate for the assay. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention

(B) Even if a protein product were to be produced, the protein product is not in any way characterized. There is no teaching in the specification or the art of record as to whether the protein product is a cell surface protein or whether it is one that is released into bodily fluids. In the absence of this information, it could not be predicted, nor could it be determined whether the antibodies of the claimed invention, against a CSG of the invention, injected into a patient would be useful for

radioimmunoscintographic imaging as taught by the specification because intracellular proteins would not be expected to bind to the labeled proteins and without release, the proteins would not be available for binding in bodily fluids. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the method would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

(C) Even if a protein were to be produced, were to be a cell surface protein or released into biological fluids, Applicant does not provide information drawn to how to differentiate between, for example, diagnosis of colon cancer by *in vivo* antibody imaging and the diagnosis of herpes virus 1 or herpes virus 3, both of which share epitopes identical to the protein encoded by SEQ ID NO:1 (see Ensser et al (T03116), Genbank Sequence Database (T03116) (us-09-762-021a-1.rpr result 9), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available 24 November 1999 and Bankier et al (A03742), Genbank Sequence Database (Accession A03742), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available 23 August 1997 (us-09-762-021a-1.rpr result 8, respectively) wherein virus infection would be expected to lead to an increased level of detected protein expression and it is not clear that colon cancer would reliably lead to an increased level of detected protein expression for the reasons set forth above.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7 Claim 1 is rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by US Patent No. 5,733,748, of record.

The claim is drawn to a method for diagnosing the presence of colon cancer comprising measuring levels of CSG proteins in cells, tissues or bodily fluids in a patient and comparing the measured levels with levels of CSG in cells, tissues or bodily fluids from a normal human control.

US Patent No. 5,733,748 teaches a method of utilizing Human Colon Specific Gene (CSG) polypeptides as a diagnostic marker for colon cancer (see abstract) wherein the diagnosis is by detecting altered levels of CSG polypeptides in a biological sample, tissue, elevated levels of CSG polypeptides, wherein the assays are well known in the art , wherein the tissue can be biological fluids, cell samples diagnosing colon cancer comprising measuring levels of CSG polypeptides (col 9,

line 52-col 4, line 3). Although the reference does not specifically teach that the levels of CSG polypeptides are elevated above normal controls, it would be reasonable to conclude, one of skill in the art would instantaneously known that the elevated levels are levels elevated above a normal control.

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
March 4, 2003